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FluMist®
(Influenza Virus Vaccine Live, Intranasal)
Safety Update

ACIP

February 21, 2007

Purpose of Today's Presentation

- Describe the original observation of wheezing/asthma in the Kaiser study
- Discuss how the recent FluMist and TIV comparative trial (CP111) further assessed wheezing/asthma
- Present supportive safety data from placebo-controlled trials in young children
- Provide a comprehensive safety summary for children within the proposed indication, and relevant data for children outside the proposed indication

AV019 Study (Kaiser): Asthma/RAD

- Placebo-controlled trial in 9,689 children 1 to 17 years
- Signal for asthma/RAD in 18-35 month olds within 42 days of vaccination (2.2% FluMist vs. 0.54% Placebo)
- Post-hoc analyses could not rule out increased risk through 59 months (0.69% FluMist vs. 0.20% placebo)
- No temporal clustering, no hospitalizations, most visits were associated with standard medications
- No increased risk in children age 5 years and older
- Not designed to prospectively assess risk of asthma

Bergen et al, Pediatr Infect Dis J 23:138, 2004
Belshe et al, Clin Infect Dis 39:920, 2004

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CP111 Pivotal Study Design

- Randomized, double-blind, multinational study
- Active-control (TIV)
- Children 6 – 59 months of age (N = 8,475)
  - All included except recent wheezing, severe asthma and immunocompromised
- Primary endpoint
  - Culture-confirmed modified CDC influenza-like illness (CDC ILI)
- Prospectively defined safety endpoint
  - Medically significant wheezing

Belshe et al, N Engl J Med 356:685, 2007

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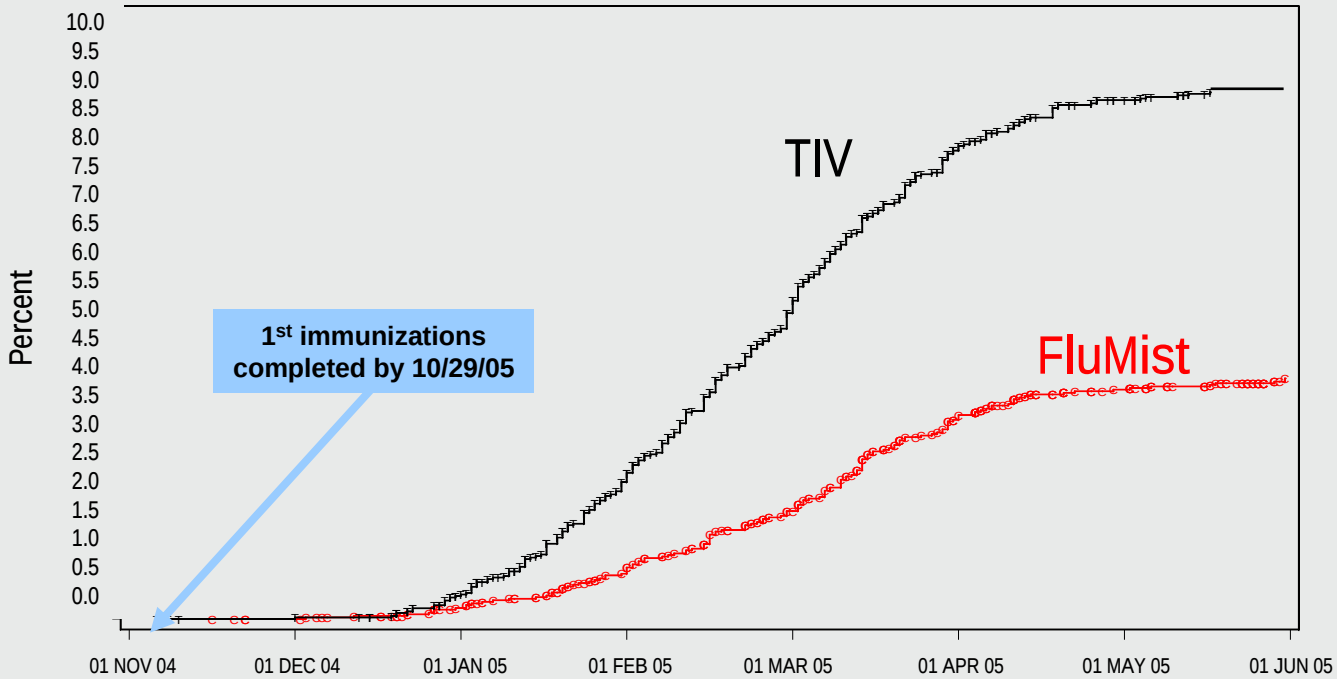
CP111 Reported Cases of Influenza

Culture-confirmed Modified CDC-ILI Influenza Caused by Any Wild-type Strain (Matched and Mismatched)



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CP111 Safety Comparisons
FluMist vs. TIV

- Rates of serious adverse events were similar
- Rates of reactogenicity events were as expected
  - FluMist ↑ runny/stuffy nose
  - TIV ↑ injection site reactions

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CP111 Medically Significant Wheezing (MSW) Comparisons

- No increased risk for FluMist in children age ≥2 years
- Statistically significant increase in children <2 years (two dose group) after dose one
  - 3.2% FluMist vs. 2.0% TIV
- The increase after dose one in children <2 years occurred primarily among those 6-11 months
  - 6-11 months: 3.8% FluMist vs. 2.1% TIV
  - 12-23 months: 2.8% FluMist vs. 2.0% TIV

CP111 MSW in Children <24 Months *Severity for FluMist and TIV*

- Proportion with tachypnea, dyspnea, retractions, or hypoxemia within 42 days after dose 1 similar
  - 27% FluMist vs. 26% TIV
- 12 children were hospitalized with MSW within 42 days after a dose
  - 9 (0.5%) FluMist vs. 3 (0.2%) TIV
  - No ICU, mechanical ventilation, or deaths because of MSW
  - Comparable illness severity based on hospital stay, discharge diagnoses, and treatment

CP111: MSW in Children <24 Months
Recurrent MSW

- Children with MSW within 42 days after last vaccination had
  - At least one additional MSW episode
    FluMist 32% vs. TIV 28%
  - Two or more additional MSW episodes
    FluMist 4.3% vs. TIV 5.3%

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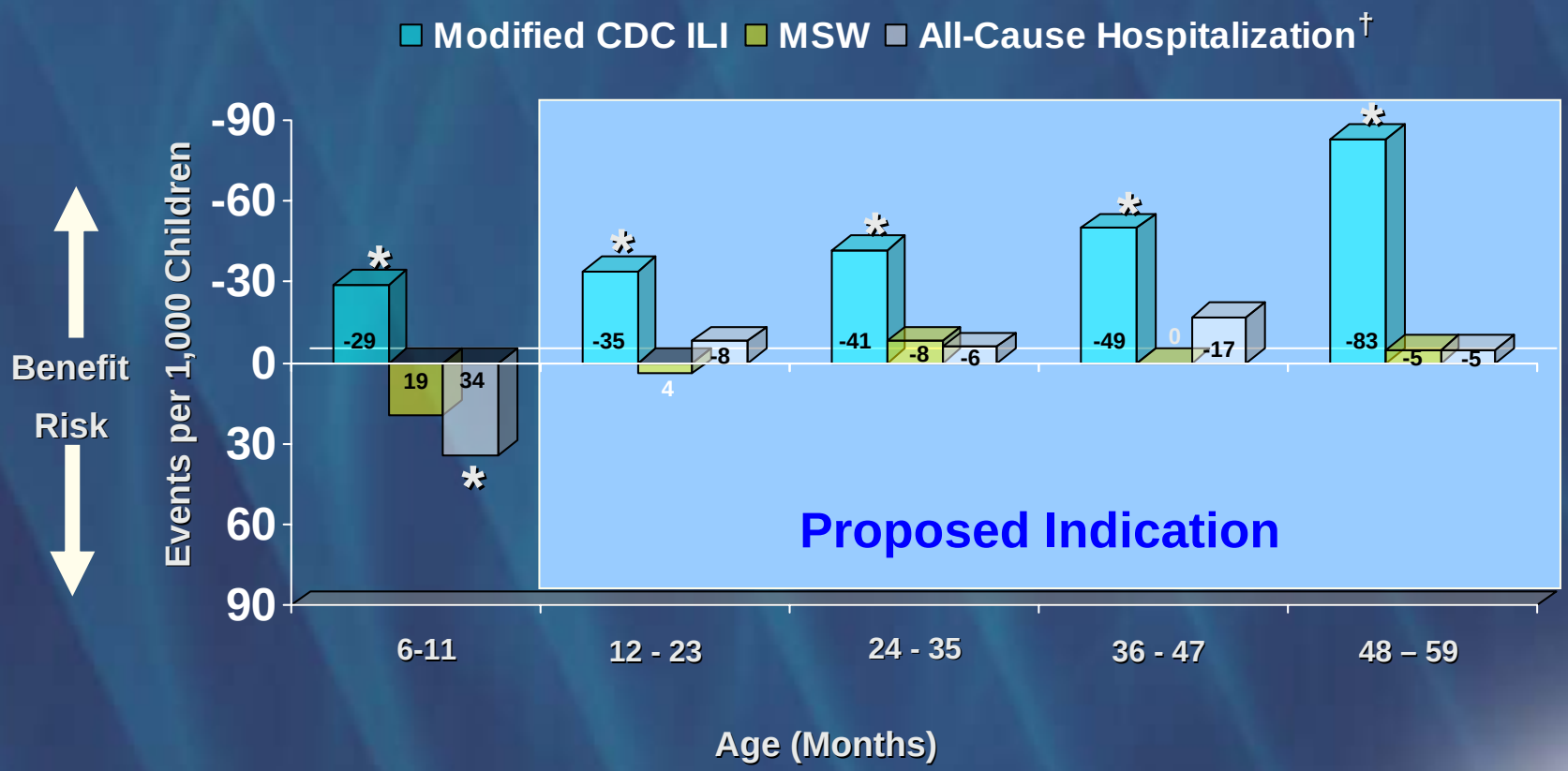
Post Hoc Risk-Benefit Analysis

- Events analyzed through 180 days after last vaccination
  - Culture confirmed modified CDC-ILI
  - Medically significant wheezing
  - All cause hospitalization
- Analysis by history of wheezing/asthma
  - “Does the subject have a past medical history of wheeze?”
  - “Has a diagnosis of asthma ever been made?”

Risk-Benefit of FluMist vs. TIV: *Children Without History of Wheezing or Asthma (N=6,580)*



† Most were common pediatric diagnoses, i.e., GI and LRT infections

* Rate Difference (FluMist – TIV) statistically significant.

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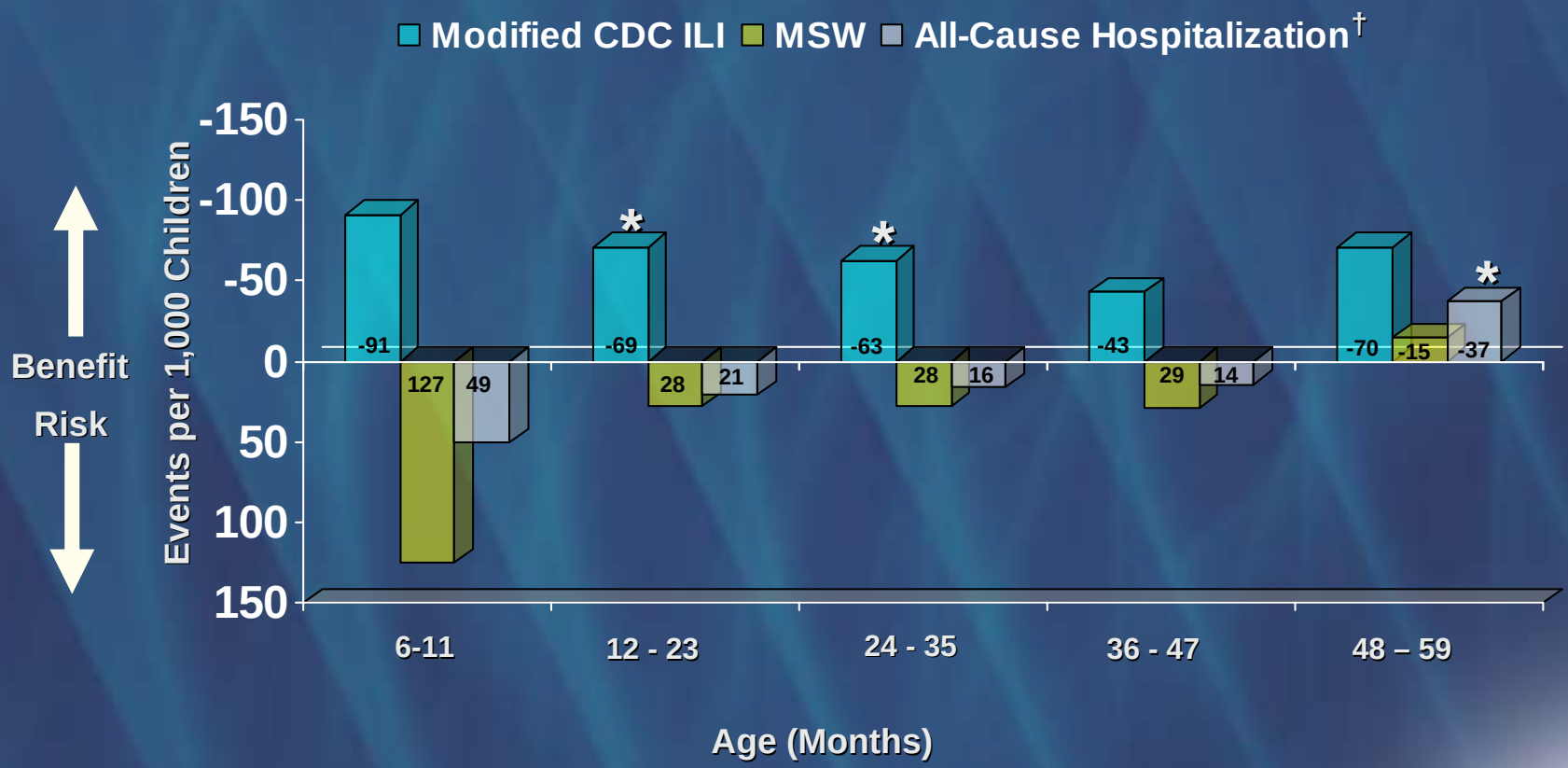
Risk-Benefit of FluMist vs. TIV: *Children With History of Wheezing or Asthma (N=1,772)*



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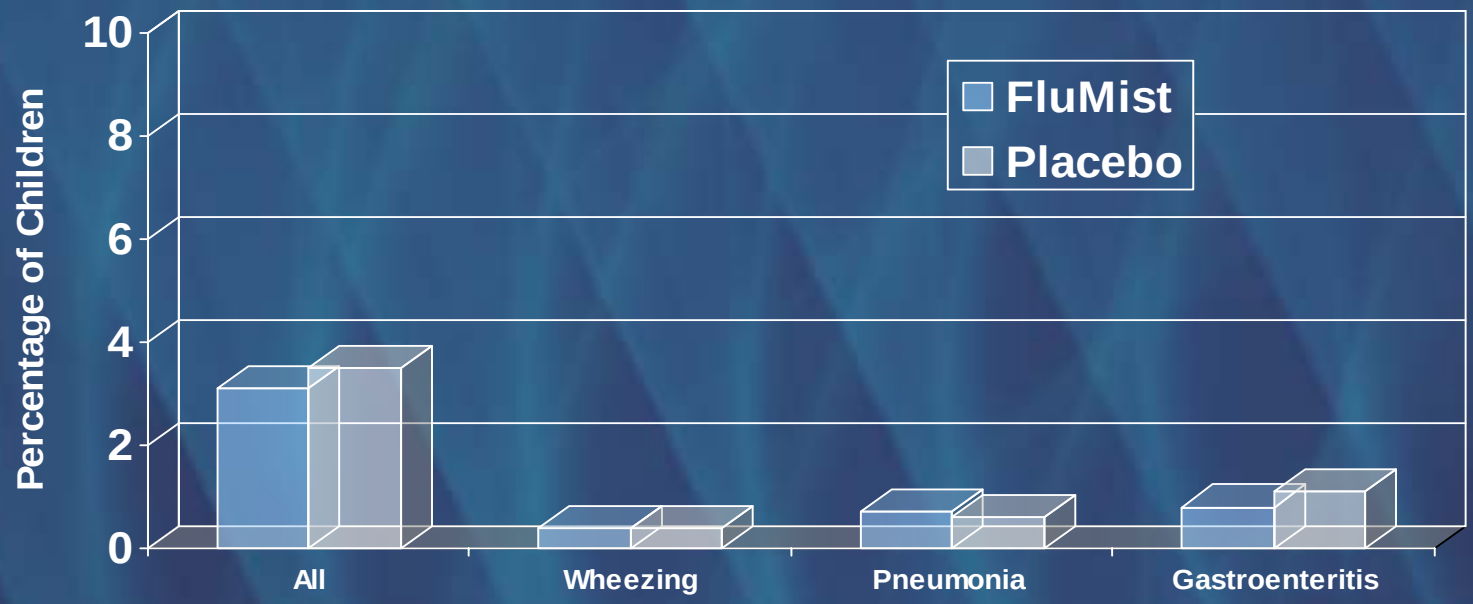
FluMist Trials in Children 6 to 59 Months of Age

- 13 clinical trials included in the safety summary provided to the FDA (N=30,114)
  - 9 placebo controlled (N=18,475)
  - 3 TIV controlled
    - CP111 (N=8,352)
    - 2 additional studies (N=1,902)
  - 1 uncontrolled (N=1,385)
- These trials provide data on rates of serious adverse events; nearly all were hospitalizations
- Analyses include all children regardless of history of wheezing/asthma

Serious Adverse Events Through 180 Days in Placebo Controlled Trials

Children 12 – 59 Months (N=12,579)



Wheezing includes the MedDRA terms wheeze, asthma, bronchospasm, bronchiolitis. Pneumonia includes the MedDRA terms bronchopneumonia, lobar pneumonia, lower respiratory tract infection, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia mycoplasmal, pneumonia parainfluenza viral, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, and pneumonitis. Gastroenteritis includes the MedDRA terms abdominal pain, diarrhea, duodenitis, enteritis, enterocolitis, gastritis, vomiting, diarrhea infectious, dysentery, gastritis viral, gastroenteritis, viral stool test positive.

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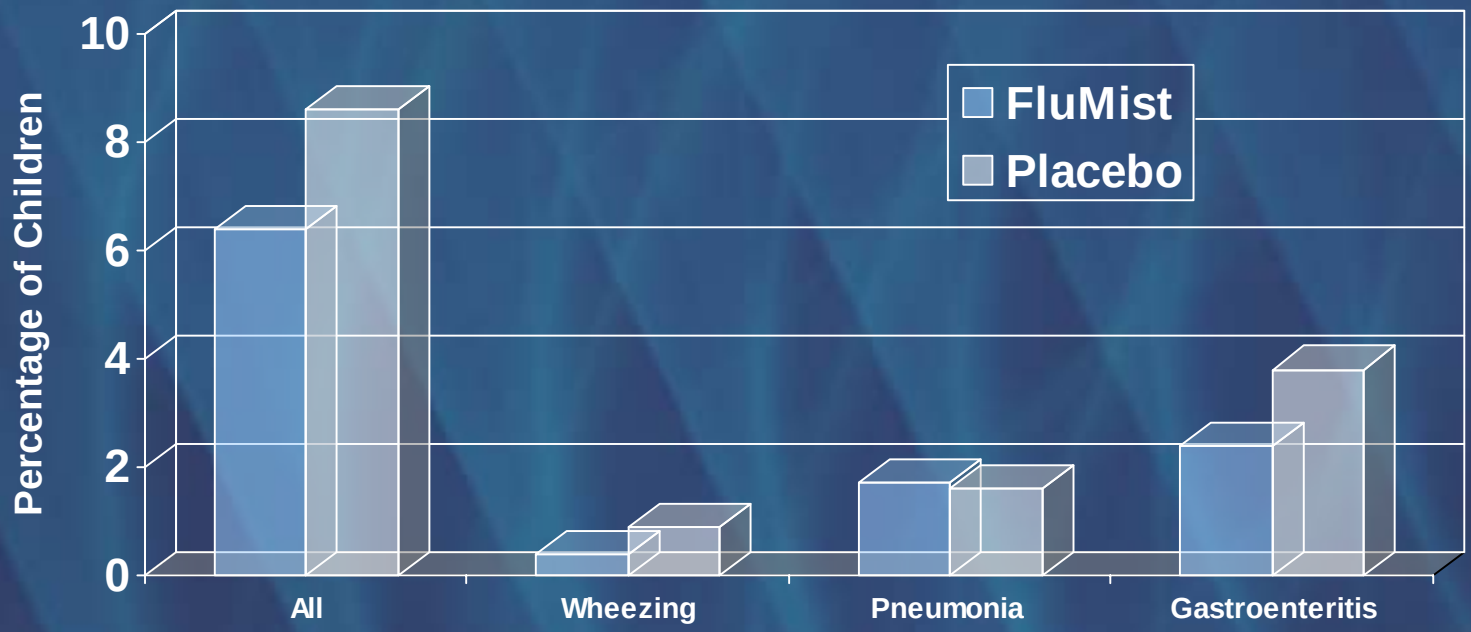
Serious Adverse Events Through 180 Days in Placebo Controlled Trials

Children 6 – 11 Months (N=1,576)



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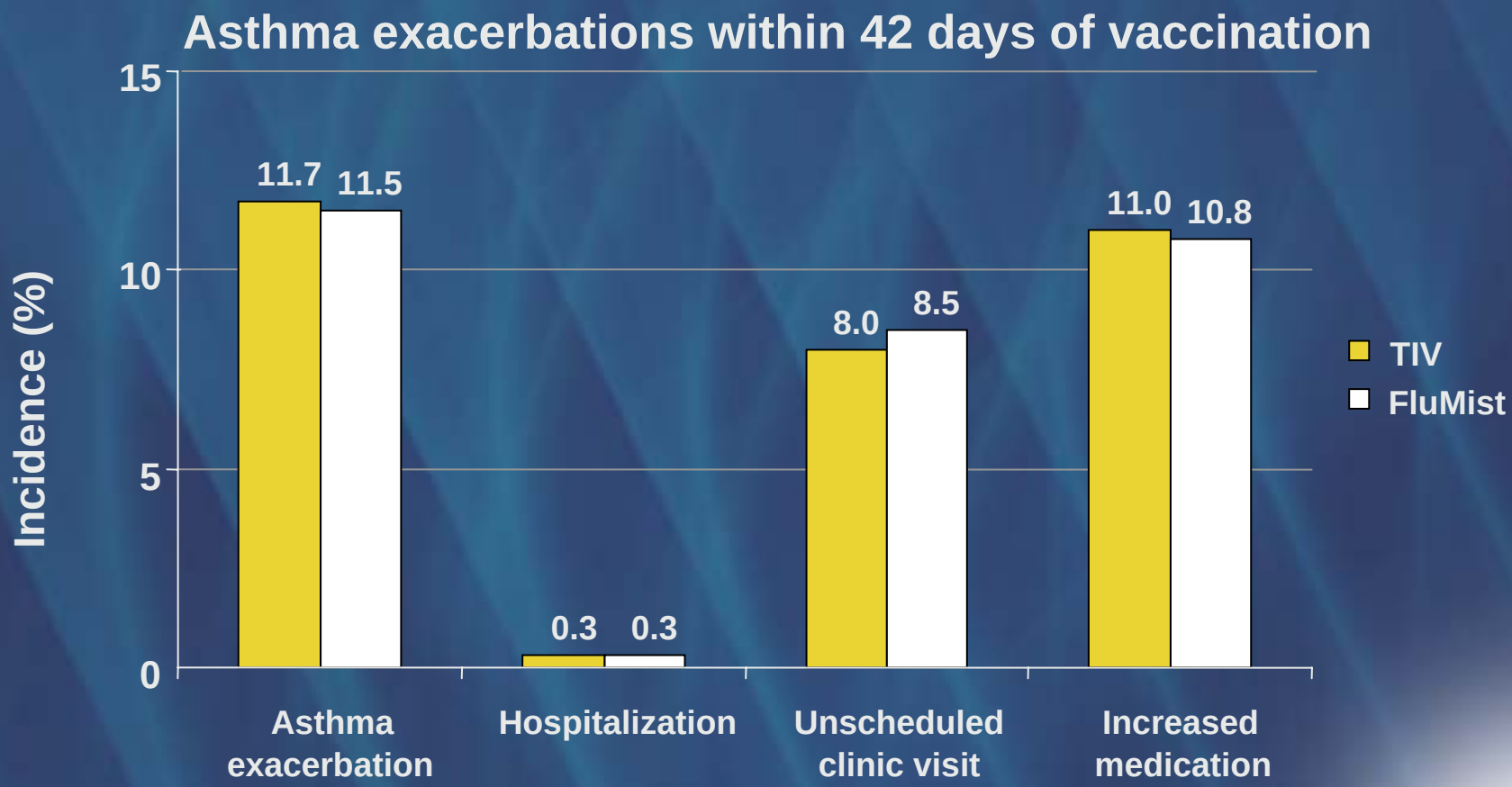
Safety of FluMist vs. TIV in Asthmatic Subjects 6 to 17 Years of Age (N= 2,229)



Fleming et al. Pediatr Infect Dis J 25:860, 2006

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Conclusions

- Superior efficacy against matched and mismatched influenza vs TIV
  - High efficacy demonstrated in 6 placebo-controlled trials
- Safety of FluMist for children <12 months, and in children <59 months with a history of wheezing/asthma needs further study

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Conclusions (continued)

- In children 12-59 months without history of wheeze or asthma, FluMist appears to have a highly favorable risk-benefit profile
  - ~80% of all children between 12-59 months in CP111
- Review of placebo-controlled trials supports the safety of FluMist in children 12-59 months
- Data to support the proposed indication in children 12-59 months without a history of wheeze or asthma are currently under regulatory review

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